

**AMENDMENTS TO THE SPECIFICATION:**

**Please replace the paragraph beginning at page 1, line 13 with the following amended paragraph:**

This application is related to ~~U.S. application Serial No. attorney dkt. No. 37851-922PC~~ PCT Application No. IB03/004347, entitled, "RATIONAL EVOLUTION OF CYTOKINES FOR HIGHER STABILITY, THE CYTOKINES AND ENCODING NUCLEIC ACID MOLECULES," to Rene Gantier, Thierry Guyon, Manuel Vega and Lila Drittanti. This application also is related to U.S. application Serial No. 10/658,355, filed ~~the same day herewith~~ September 08, 2003, entitled "RATIONAL DIRECTED PROTEIN EVOLUTION USING TWO-DIMENSIONAL RATIONAL MUTAGENESIS SCANNING," and to U.S. provisional application Serial No. 60/457,063, entitled "RATIONAL DIRECTED PROTEIN EVOLUTION USING TWO-DIMENSIONAL RATIONAL MUTAGENESIS SCANNING," filed March 21, 2003, and to U.S. provisional application Serial No. 60/410,258, entitled "RATIONAL DIRECTED PROTEIN EVOLUTION USING TWO-DIMENSIONAL RATIONAL MUTAGENESIS SCANNING," filed September 9, 2002, each to Rene Gantier, Thierry Guyon, Hugo Cruz Ramos, Manuel Vega and Lila Drittanti. This application also is related to co-pending U.S. application Serial No. 10/022,249, filed December 17, 2001, entitled "HIGH THROUGHPUT DIRECTED EVOLUTION BY RATIONAL MUTAGENESIS," to Manuel Vega and Lila Drittanti.

**Please replace Table 5, beginning at page 145 – page 147, with the following amended Table 5:**

Mutants	SEQ ID No.	HITs (viral activity)	Pseudo wt (viral activity)
D2A	2	Decreased	
P4A	3		Pseudo wt
Q5A	4		Pseudo wt
T6A	5		Pseudo wt
H7A	6	Decreased	
S8A	7	Decreased	
L9A	8		Pseudo wt
G10A	9		Pseudo wt
S11A	10	Decreased	
R12A	11	Decreased	
R13A	12	Decreased	

Applicant : Rene Gantier *et al.*  
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T14A	13	Decreased	
L15A	14	Decreased	
M16A	15	Decreased	
L17A	16		Pseudo wt
Q20A	17		Pseudo wt
R23A	18	Decreased	
I24A	19		Pseudo wt
S25A	20		Pseudo wt
L26A	21	Decreased	
S28A	22	Decreased	
C29A	23	Decreased	
L30A	24	Decreased	
K31A	25	Decreased	
D32A	26	Decreased	
R33A	27	Decreased	
D35A	28		Pseudo wt
G37A	29		Pseudo wt
G39A	30		Pseudo wt
E41A	31		Pseudo wt
[[E42]] E42A	32		Pseudo wt
F43A	33	Decreased	
N45A	34	Decreased	
F47A	35	Decreased	
E51A	36		Pseudo wt
T52A	37		Pseudo wt
I53A	38	Decreased	
P54A	39		Pseudo wt
V55A	40		Pseudo wt
L56A	41		Pseudo wt
H57A	42		Pseudo wt
E58A	43		Pseudo wt
M59A	44	Decreased	
I60A	45		Pseudo wt
I63A	46		Pseudo wt
F64A	47		Pseudo wt
N65A	48		Pseudo wt
L66A	49	Decreased	
F67A	50	Decreased	
T69A	51	Decreased	
K70A	52	Decreased	
D71A	53	Decreased	
S72A	54	Decreased	
W76A	55		Pseudo wt
D77A	56		Pseudo wt
E78A	57		Pseudo wt
L81A	58		Pseudo wt
D82A	59	Decreased	
K83A	60	Decreased	

F84A	61	Decreased	
Y85A	62		Pseudo wt
Y89A	63		Pseudo wt
Q90A	64		Pseudo wt
[[Q91]] Q91A	65	Decreased	
N93A	66	Decreased	
D94A	67	Decreased	
C98A	68	Decreased	
V99A	69	Decreased	
Q101A	[[207]]	Decreased	
G104A	70		Pseudo wt
L110A	71		Pseudo wt
S115A	72		Pseudo wt
Y122A	73	Decreased	
W140A	74	Decreased	
E146A	75		Pseudo wt

Please replace Table 7, beginning at page 148 – page 149, with the following amended Table 7:

Mutant	SEQ ID No.	Proteolysis protection	IFN antiviral activity
E41H	88	Pseudo wt	Increased
Y89H	1303	Pseudo wt	Pseudo wt
<del>E41H/Y89H/</del> N45D** <u>E41H/Y89H/N45D</u>	979	Increased	Increased
E58Q	89	Increased	Pseudo wt
F27V	83	Pseudo wt	Pseudo wt
E58Q/F27V	981	Increased	Pseudo wt
R125H	106	Increased	Increased
M111V	978	Pseudo wt	Pseudo wt
R125H/M111V	986	Increased	Increased
E159H	125		
Y89H	1303		
E159H/Y89H	987		
K121Q	104	Increased	Pseudo wt
P109A	97	Pseudo wt	Pseudo wt
K133Q	114	Increased	Increased
K121Q/P109A	983	Increased	Pseudo wt
K121Q/P109A / K133Q / G102R	984	Increased	Increased
E78H	93	Increased	Increased
R33H	86	Pseudo wt	Pseudo wt
E58H	[[89]] 90	Increased	Increased
L110V	98	Pseudo wt	Pseudo wt
E78H/R33H/	982	Decreased	Decreased

E58H/L110V			
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**Please replace the paragraph beginning at page 151, line 11 with the following amended paragraph:**

**Screening and *in vitro* ~~eharaterization~~ characterization of IFN  $\beta$  mutants**

Two activities were measured directly on IFN samples: antiviral and antiproliferation activities. Dose (concentration) - response (activity) experiments for antiviral or antiproliferation activity allowed for the calculation of the "potency" for antiviral and antiproliferation activities, respectively. Antiviral and antiproliferation activities also were measured after incubation with proteolytic samples such as specific proteases, mixtures of selected proteases, human serum or human blood. Assessment of activity following incubation with proteolytic samples allowed to determine the residual (antiviral or antiproliferation) activity and the respective kinetics of half-life upon exposure to proteases.